

# Towards an Enantioselective Catalytic Claisen Rearrangement: Development of the First Asymmetric Acyl–Claisen Reaction

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## Supporting Information

**General Information.** All reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use according to the guidelines of Perrin and Armarego.<sup>1</sup> Non-aqueous reagents were transferred under nitrogen by syringe. Organic solutions were concentrated under reduced pressure using a Buchi rotary evaporator. Methylene chloride and *N,N*-diisopropylethylamine were distilled from calcium hydride immediately prior to use. Chlorobenzene was used as supplied by Acros. (*R,R*)-1,2-bis(2-phenyloxazolin-4-yl)benzene was prepared as described by Bolm and coworkers.<sup>2</sup> Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.<sup>3</sup> Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or KMnO<sub>4</sub> stain.

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker DRX-500 (500 MHz and 125 MHz, respectively), AMX-400 (400 MHz and 100 MHz), AMX-300 (300 MHz and 75 MHz), Varian I500 (500 MHz and 125 MHz), or Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for <sup>1</sup>H NMR are reported as follows: chemical shift ( $\delta$  ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant

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<sup>1</sup>Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3<sup>rd</sup> ed., Pergamon Press, Oxford, 1988.

<sup>2</sup>Bolm, C.

(Hz) and assignment. Data for  $^{13}\text{C}$  NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 1600 Series spectrometer using NaCl salt plates, and reported in terms of frequency of absorption ( $\text{cm}^{-1}$ ). Mass spectra were obtained from the UC Irvine Mass Spectral Facility. Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25°C). Gas chromatography was performed on Hewlett-Packard 5890A and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using the following columns: Bodman Chiraldex  $\Gamma$ -TA (30 m x 0.25 mm) and C&C Column Technologies CC-1701 (30 m x 0.25 mm). HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at 254nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm), OJ (25 cm) and OJ guard (5 cm).

**(*R,R*)-1,2-Dichloro-4,5-bis(2-phenyloxazolin-4-yl)benzene** ( $\text{ArCl}_2$ -PhBox **2b**). A solution of 4,5-dichloro-1,2-phthalonitrile (500 mg, 2.5 mmol), (*R*)-phenylglycinol (1.04 g, 7.6 mmol), and anhydrous  $\text{ZnCl}_2$  (17 mg, 130  $\mu\text{mol}$ ) in chlorobenzene (9 mL) was warmed to reflux for 12 h. After cooling to room temperature, the solvent was removed by rotary evaporation, and the residue was partitioned between  $\text{CH}_2\text{Cl}_2$  (15 mL) and water (15 mL). The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), concentrated, and purified by flash chromatography (66:33 hexanes:EtOAc) to afford 579 mg (1.32 mmol, 52% yield) of **2b** as a viscous yellow oil. IR (thin film) 3061, 3030, 2898, 1652, 1505, 1488, 1393, 1034  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26-7.33 (m, 10H, PhH), 6.07 (s, 2H, ClPhH), 5.32 (dd,  $J = 9.2, 9.2$  Hz, 2H,  $\text{OCH}_2\text{CHN}$ ), 4.67 (dd,  $J = 8.5, 9.9$  Hz, 2H,  $\text{OCH}_2\text{CHN}$ ), 4.16 (dd,  $J = 8.2, 8.5$  Hz, 2H,  $\text{OCH}_2\text{CHN}$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  149.5, 142.4, 128.8, 128.6, 127.7, 127.1, 110.5, 102.5, 75.5, 70.8; HRMS (FAB) exact mass calcd for ( $\text{C}_{24}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_2 + \text{H}^+$ ) requires  $m/z$  437.0824, found  $m/z$  437.0817.  $[\alpha]_{\text{D}} = +68.1$  ( $c = 1.0, \text{CHCl}_3$ ).

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<sup>3</sup>Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

**(*R,R*)-1,2-Dichloro-4,5-bis(2-(*p*-methoxyphenyl)oxazolin-4-yl)benzene** (ArCl<sub>2</sub>-PMPBox **2c**).

(*R*)-(*p*-Methoxyphenyl)glycinol was prepared as previously described.<sup>4</sup> A solution of 4,5-dichloro-1,2-phthalonitrile (2.4 g, 12 mmol), (*R*)-(*p*-methoxyphenyl)glycinol (5.0 g, 30 mmol), and anhydrous ZnCl<sub>2</sub> (160 mg, 1.2 mmol) in chlorobenzene (120 mL) was warmed to reflux for 7 h. After cooling to room temperature, the solvent was removed by rotary evaporation, and the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and H<sub>2</sub>O (15 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified by flash chromatography (66:33 to 50:50 hexanes:EtOAc gradient). The resulting solid was recrystallized from EtOAc and hexanes to give 4.0 g (8.0 mmol, 67%) of **2c** a white crystalline material. IR (thin film) 1955, 1906, 1833, 1669, 1649, 1514, 1247, 951, 832 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.96 (s, 2H, ClPhH), 7.24 (d, *J* = 8.8 Hz, 4H, MeOPhH), 6.82 (d, *J* = 8.8 Hz, 4H, MeOPhH), 5.30 (dd, *J* = 8.5, 9.9 Hz, 1H, OCH<sub>2</sub>CHN), 4.67 (dd, *J* = 8.5, 10.2 Hz, 2H, OCH(H)CHN), 4.18 (dd, *J* = 8.5, 8.5 Hz, 2H, OCH(H)CHN), 3.78 (s, 6H, OCH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 162.6, 159.0, 134.9, 133.8, 131.8, 128.0, 127.9, 114.0, 75.6, 70.1, 55.3; HRMS (CI) exact mass calcd for (C<sub>26</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>)<sup>+</sup> requires *m/z* 496.0957, found *m/z* 496.0956; [α]<sub>D</sub> = +72.9 (*c* = 1.0, CHCl<sub>3</sub>).

**General Procedure.** To a flask charged with ArCl<sub>2</sub>-PMPBox **2c** and anhydrous MgI<sub>2</sub> in an inert atmosphere, was added CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and the resulting pale yellow solution was stirred vigorously for 1 h under an inert atmosphere. The allyl morpholine (0.4 mmol) was then added via syringe as a solution in CH<sub>2</sub>Cl<sub>2</sub> (1 mL). The syringe was rinsed with CH<sub>2</sub>Cl<sub>2</sub> (3 x 1 mL), and the combined rinses were added to the reaction flask. The reaction mixture was then treated with *i*-Pr<sub>2</sub>NEt, then cooled to -20 °C. At this point, a solution of the acid chloride (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>) was added over 12 h. After a further 12 hours at -20 °C, the reaction mixture was washed with a mixture of EtOAc (25 mL) and 1 N NaOH (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were then washed with saturated aq. NaCl (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and then concentrated. The resulting residue was then added to EtOH (15 mL) and set aside. After 6-10 h, the precipitated

<sup>4</sup> Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, 50, 9457.

ArCl<sub>2</sub>-PMPBox ligand was removed by filtration, and the resulting supernatant solution was concentrated by rotary evaporation. The resulting residue was then purified by preparative HPLC or by flash chromatography.

**(2S)-N-(2-Benzyloxy-4-pentenoyl)-morpholine** (Table 1, Entry 6) Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and benzyloxyacetyl chloride (0.48 mL, 1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 0.48 mmol), using MgI<sub>2</sub> (222 mg, 0.80 mmol), ArCl<sub>2</sub>-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr<sub>2</sub>NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 80% yield (88 mg, 0.32 mmol); 91% ee. IR (thin film) 2916, 2854, 1643, 1457, 1436, 1114 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.27-7.37 (m, 5H, PhH), 5.83 (ddd, *J* = 7.0, 10.2, 17.1 Hz, 1H, CH=CH<sub>2</sub>), 5.10-5.17 (m, 2H, CH=CH<sub>2</sub>), 4.62 (d, *J* = 11.7 Hz, 1H, CH<sub>2</sub>Ph), 4.45 (d, *J* = 11.7 Hz, 1H, CH<sub>2</sub>Ph), 6.54 (dd, *J* = 6.0, 8.0 Hz, 1H, CHOCH<sub>2</sub>Ph), 3.57-3.83 (m, 8H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 2.47-2.62 (m, 2H, CH<sub>2</sub>CH=CH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.6, 137.3, 133.4, 128.5, 128.0, 128.0, 118.0, 79.0, 71.4, 67.1, 66.8, 45.7, 42.6, 36.7; HRMS (CI) exact mass calcd for (C<sub>16</sub>H<sub>21</sub>NO<sub>3</sub> + H<sup>+</sup>) requires *m/z* 276.1599, found *m/z* 276.1594; [α]<sub>D</sub> = +30.2 (*c* = 1.0, CHCl<sub>3</sub>).

The enantiomeric purity was determined by HPLC with a Chiralcel OJ column and OJ guard column (10% EtOH:hexanes, 1 mL/min flow); *t*<sub>r</sub> = 16.8 min and 19.3 min.

**(2S)-N-(2-Methoxy-4-pentenoyl)-morpholine** (Table 2, Entry 5) Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and methoxyacetyl chloride (0.48 mL, 1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 0.48 mmol), using MgI<sub>2</sub> (222 mg, 0.80 mmol), ArCl<sub>2</sub>-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr<sub>2</sub>NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 28% yield (22 mg, 0.11 mmol); 80% ee. IR (thin film) 2946, 2853, 2812, 1721, 1659, 1119 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.81 (ddd, *J* = 7.0, 10.2, 17.1 Hz, 1H, CH=CH<sub>2</sub>), 5.09-5.16 (m, 2H, CH=CH<sub>2</sub>), 4.07 (dd, *J* = 6.0, 7.8 Hz, 1H, CHOCH<sub>3</sub>), 3.64-3.78 (m, 8H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 3.35 (s, 3H, CH<sub>3</sub>), 2.44-2.55 (m, 2H, CH<sub>2</sub>CH=CH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.5, 133.4, 117.9, 81.1, 67.1, 66.9, 56.9, 45.6, 42.6,

36.4; HRMS (CI) exact mass calcd for ( $\text{C}_{10}\text{H}_{17}\text{NO}_3^+$ ) requires  $m/z$  199.1208, found  $m/z$  199.1211;  $[\alpha]_{\text{D}} = +2.1$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

The enantiomeric purity was assayed by derivitization of a portion of the product to the iodolactone ( $\text{I}_2$ , 1:1  $\text{H}_2\text{O}$ :DME, 15 min) and analysis by GC with a Bodman ChiralDEX  $\Gamma$ -TA column (50  $^\circ\text{C}$ , 1  $^\circ\text{C}/\text{min}$  gradient, 1 mL/min); minor diastereomer,  $t_{\text{r}} = 92.9$  min and 107.7 min.

**(2S)-N-(2-Phenoxy-4-pentenoyl)-morpholine** (Table 2, Entry 4) Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and phenoxyacetyl chloride (0.48 mL, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 0.48 mmol), using  $\text{MgI}_2$  (222 mg, 0.80 mmol),  $\text{ArCl}_2$ -PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr<sub>2</sub>NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 48% yield (50 mg, 0.19 mmol); 78% ee. IR (thin film) 3072, 2968, 2916, 2854, 1643, 1597, 1228  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25-7.29 (m, 2H, PhH), 6.96-7.00 (m, 1H, PhH), 6.89 (d,  $J = 8.8$  Hz, 2H, PhH), 5.88 (ddd,  $J = 7.0, 10.0, 17.0$  Hz, 1H,  $\text{CH}=\text{CH}_2$ ), 5.14-5.22 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 4.85 (dd,  $J = 6.5, 7.5$  Hz, 1H,  $\text{CH}_2\text{OPh}$ ), 3.36-3.78 (m, 8H,  $\text{N}(\text{CH}_2\text{CH}_2)_2$ ), 2.70-2.72 (m, 2H,  $\text{CHCH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.8, 157.2, 132.7, 129.8, 121.8, 118.5, 114.9, 78.5, 67.0, 66.7, 45.8, 42.9, 36.8; HRMS (CI) exact mass calcd for ( $\text{C}_{15}\text{H}_{19}\text{NO}_3 + \text{H}^+$ ) requires  $m/z$  262.1443, found  $m/z$  262.1438;  $[\alpha]_{\text{D}} = -26.3$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ). The enantiomeric purity was determined by HPLC with a Chiralcel OJ column and OJ guard column (3% EtOH:hexanes, 1 mL/min flow);  $t_{\text{r}} = 28.3$  min and 32.6 min.

**(2S)-N-(2-(*p*-Chlorophenoxy)-4-pentenoyl)-morpholine** (Table 2, Entry 3) Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and (*p*-chlorophenoxy)acetyl chloride (0.48 mL, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 0.48 mmol), using  $\text{MgI}_2$  (222 mg, 0.80 mmol),  $\text{ArCl}_2$ -PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr<sub>2</sub>NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 59% yield (70 mg, 0.24 mmol); 71% ee. IR (thin film) 3072, 2968, 2916, 2854, 1643, 1597, 1493, 1234  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23 (d,  $J = 9.0$  Hz, 1H, PhH), 6.83 (d,  $J = 9.0$  Hz, 1H, PhH), 5.87 (ddd,  $J = 7.0, 10.0, 17.0$  Hz, 1H,  $\text{CH}=\text{CH}_2$ ), 5.15-5.23 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 4.80 (dd,  $J = 6.2, 7.5$  Hz, 1H,  $\text{CH}-$

O(PhCl)), 3.39-3.75 (m, 8H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 2.68-2.76 (m, 2H, CHCH=CH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.4, 155.8, 132.4, 129.7, 118.7, 116.2, 114.9, 78.9, 67.0, 66.7, 45.8, 42.9, 36.7; HRMS (CI) exact mass calcd for (C<sub>15</sub>H<sub>18</sub>NO<sub>3</sub>Cl<sup>+</sup>) requires *m/z* 295.0975, found *m/z* 295.0969; [α]<sub>D</sub> = −17.7 (c = 1.0, CHCl<sub>3</sub>).

The enantiomeric purity was determined by HPLC with a Chiralcel AD column and AD guard column (3% *i*-PrOH:hexanes, 1 mL/min flow); t<sub>r</sub> = 36.2 min and 41.8 min.

**(2S)-N-(2-Acetoxy-4-pentenoyl)-morpholine** (Table 2, Entry 1) Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and acetoxyacetyl chloride (0.48 mL, 1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 0.48 mmol), using MgI<sub>2</sub> (222 mg, 0.80 mmol), ArCl<sub>2</sub>-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr<sub>2</sub>NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 44% yield (40 mg, 0.18 mmol); 37% ee. IR (thin film) 2968, 2926, 2864, 1737, 1654, 1451, 1239 cm<sup>−1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.74 (ddd, *J* = 7.1, 10.1, 17.1 Hz, 1H, CH=CH<sub>2</sub>), 5.29 (m, 1H, CHOAc), 5.11-5.13 (m, 2H, CH=CH<sub>2</sub>), 3.48-3.69 (m, 8H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 2.48-2.57 (m, 2H, CH<sub>2</sub>CH=CH<sub>2</sub>), 2.10 (s, 3H, OAc); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.0, 168.2, 132.3, 119.3, 69.6, 67.2, 66.8, 46.4, 42.8, 36.0, 21.0; HRMS (CI) exact mass calcd for (C<sub>11</sub>H<sub>17</sub>NO<sub>4</sub><sup>+</sup>) requires *m/z* 227.1158, found *m/z* 257.1152; [α]<sub>D</sub> = −4.3 (c = 1.0, CHCl<sub>3</sub>).

The enantiomeric purity was assayed by derivitization of a portion of the product to the deprotected secondary alcohol (NaBH<sub>4</sub>, MeOH, 2 h) and analysis by GC with a Bodman Chiraldex Γ-TA column (70 °C, 3 °C/min gradient, 1 mL/min); minor diastereomer, t<sub>r</sub> = 34.6 min and 35.9 min.

**(2S)-N-(2-(*t*-Butyldimethylsilyloxy)-4-pentenoyl)-morpholine** (Table 2, Entry 2) Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and (*t*-butyldimethylsilyl)oxyacetyl chloride (0.48 mL, 1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 0.48 mmol), using MgI<sub>2</sub> (222 mg, 0.80 mmol), ArCl<sub>2</sub>-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr<sub>2</sub>NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 67% yield (81 mg, 0.27 mmol); 38% ee. IR (thin film) 5/77, 2911, 2854, 1643, 1462, 1436, 1249,

839  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.75 (ddd, 7.0, 10.1, 17.2 Hz, 1H,  $\text{CH}=\text{CH}_2$ ), 5.06-5.10 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 4.38-4.45 (m, 1H,  $\text{CH}-\text{OTBS}$ ), 3.56-3.85 (m, 8H,  $\text{N}(\text{CH}_2\text{CH}_2)_2$ ), 2.24-2.45 (m, 2H,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 0.86 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.04 (s, 4H,  $\text{Si}(\text{CH}_3)_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 133.5, 118.1, 75.7, 67.1, 67.0, 45.9, 42.7, 39.9, 25.7, 18.1, -4.7, -5.2; HRMS (CI) exact mass calcd for ( $\text{C}_{15}\text{H}_{29}\text{NO}_3\text{Si} + \text{H}^+$ ) requires  $m/z$  300.1995, found  $m/z$  300.1986;  $[\alpha]_{\text{D}} = +6.2$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

The enantiomeric purity was assayed by derivitization of a portion of the product to the deprotected secondary alcohol (2N HCl, MeOH, 30 min) and analysis by GC with a Bodman Chiraldex  $\Gamma$ -TA column (70  $^\circ\text{C}$ , 3  $^\circ\text{C}/\text{min}$  gradient, 1 mL/min); minor diastereomer,  $t_{\text{r}} = 34.5$  min and 35.8 min.

**(2S)-N-(2-Benzyloxy-5-methyl-4-pentenoyl)-morpholine** (Table 3, Entry 2) Prepared by the general procedure from *N*-methallyl morpholine (57 mg, 0.40 mmol) and benzyloxyacetyl chloride (0.48 mL, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 0.48 mmol), using  $\text{MgI}_2$  (222 mg, 0.80 mmol),  $\text{ArCl}_2$ -PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr<sub>2</sub>NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 78% yield (90 mg, 0.31 mmol); 91% ee. IR (thin film) 3072, 3030, 2968, 2916, 2854, 1643, 1457, 1436  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21–7.34 (m, 5H, PhH), 4.83 (s, 1H,  $\text{CMe}=\text{CH}_2$ ), 4.77 (s,  $\text{CMe}=\text{CH}_2$ ), 4.60 (d, 1H,  $J = 11.6$  Hz, 1H,  $\text{CH}_2\text{Ph}$ ), 4.43 (d, 1H,  $J = 11.6$  Hz, 1H,  $\text{CH}_2\text{Ph}$ ), 4.33 (dd,  $J = 5.5$ , 8.7 Hz, 1H,  $\text{CHOCH}_2\text{Ph}$ ), 3.56-3.75 (m, 8H,  $\text{N}(\text{CH}_2\text{CH}_2)_2$ ), 2.52 (dd,  $J = 8.7$ , 14.3 Hz, 1H,  $\text{CH}_2\text{CMe}=\text{CH}_2$ ), 2.41 (dd,  $J = 5.4$ , 14.3 Hz, 1H,  $\text{CH}_2\text{CMe}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 141.1, 137.3, 128.5, 128.0, 128.0, 113.6, 78.5, 71.6, 67.1, 66.8, 45.7, 42.5, 40.6, 22.5; HRMS (CI) exact mass calcd for ( $\text{C}_{17}\text{H}_{23}\text{NO}_3 + \text{H}^+$ ) requires  $m/z$  290.1756, found  $m/z$  290.1764;  $[\alpha]_{\text{D}} = +30.0$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

The enantiomeric purity was determined by HPLC with a Chiralcel OJ column and OJ guard column (6% *i*-PrOH:hexanes, 1 mL/min flow);  $t_{\text{r}} = 14.8$  min and 16.4 min.

**(2S)-N-(2-Benzyloxy-5-phenyl-4-pentenoyl)-morpholine** (Table 3, Entry 3) Prepared by the general procedure from *N*-(2-phenyl-2-propenyl)morpholine (81 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 1.0 mmol), using  $\text{MgI}_2$  (334 mg, 1.2 mmol),  $\text{ArCl}_2$ -PMPBox

**2c** (597 mg, 1.2 mmol), and *i*-Pr<sub>2</sub>NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 79% yield (111 mg, 0.32 mmol); 90% ee. IR (thin film) 3030, 1926, 1854, 1716, 1643, 1509, 1451, 1244 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.20-7.40 (m, 10H, PhH), 5.39 (d, *J* = 1.4 Hz, CPh=CH<sub>2</sub>), 5.20 (d, *J* = 1.1 Hz, CPh=CH<sub>2</sub>), 4.55 (d, *J* = 11.5 Hz, 1H, CH<sub>2</sub>Ph), 4.35 (d, *J* = 11.5 Hz, 1H, CH<sub>2</sub>Ph), 4.28 (dd, *J* = 6.9, 7.1 Hz, 1H, CHOCH<sub>2</sub>Ph), 3.42-3.63 (m, 8H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 3.00 (dd, *J* = 0.8, 6.9 Hz, 2H, CH<sub>2</sub>CPh=CH<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 169.6, 143.5, 139.9, 137.1, 128.3, 128.2, 127.8, 127.6, 126.0, 115.8, 99.9, 77.0, 71.4, 67.0, 66.6, 45.6, 42.4, 38.5; HRMS (CI) exact mass calcd for (C<sub>22</sub>H<sub>25</sub>NO<sub>3</sub> + H<sup>+</sup>) requires *m/z* 352.1912, found *m/z* 352.1912; [α]<sub>D</sub> = +4.9 (*c* = 1.0, CHCl<sub>3</sub>).

The enantiomeric purity was determined by HPLC with a Chiralcel AD column and AD guard column (10% *i*-PrOH:hexanes, 1 mL/min flow); *t*<sub>r</sub> = 13.4 min and 16.0 min.

**(2*S*,3*R*)-*N*-(2-Benzoyloxy-3-(benzoyloxymethyl)-4-pentenoyl)-morpholine** (Table 3, Entry 4)

Prepared by the general procedure from (*E*)-*N*-(4-benzoyloxy-2-butenyl)morpholine (105 mg, 0.40 mmol) and benzoyloxyacetyl chloride (0.48 mL, 1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 0.48 mmol), using MgI<sub>2</sub> (222 mg, 0.80 mmol), ArCl<sub>2</sub>-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr<sub>2</sub>NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 86% yield (140 mg, 0.34 mmol); *syn:anti* 92:8; 86% ee. *Syn* isomer: IR (thin film) 3072, 3030, 2968, 2916, 2854, 1716, 1643, 1451, 1275 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.94 (d, *J* = 7.1 Hz, 2H, C(O)PhH), 7.53 (t, *J* = 7.4 Hz, 1H, C(O)PhH), 7.39 (dd, *J* = 7.9, 7.5 Hz, 2H, C(O)PhH), 7.18-7.28 (m, 5H, CH<sub>2</sub>(PhH)), 5.78 (ddd, *J* = 9.3, 10.2, 17.1 Hz, 1H, , CH=CH<sub>2</sub>), 5.15-5.21 (m, 2H, CH=CH<sub>2</sub>), 4.65 (d, *J* = 11.7 Hz, 1H, CH<sub>2</sub>Ph), 4.49-4.51 (m, 2H, CH<sub>2</sub>OBz), 4.42 (d, *J* = 11.7 Hz, 1H, CH<sub>2</sub>Ph), 4.27 (d, *J* = 9.5 Hz, 1H, CHOBn), 3.54-3.73 (m, 8H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 2.91-2.96 (m, 1H, CH=CH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.6, 166.3, 136.8, 134.0, 133.0, 130.0, 129.6, 129.5, 128.5, 128.4, 128.2, 128.2, 120.3, 97.4, 72.3, 67.1, 66.7, 64.5, 46.7, 45.6, 42.6; HRMS (CI) exact mass calcd for (C<sub>24</sub>H<sub>27</sub>NO<sub>5</sub> + H<sup>+</sup>) requires *m/z* 410.1967, found *m/z* 410.1952; [α]<sub>D</sub> = +8.6 (*c* = 1.0, CHCl<sub>3</sub>).



The enantiomeric purity and diastereomer ratio were determined by HPLC with a Chiralcel OD-H column and OD guard column (10% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer,  $t_r$  = 20.1 min and 29.5 min; *anti* isomer,  $t_r$  = 23.2 min and 26.0 min.

**(2*S*,3*S*)-*N*-(2-Benzoyloxy-3-(*p*-nitrophenyl)-4-pentenoyl)-morpholine** (Table 3, Entry 5)

Prepared by the general procedure from (*E*)-*N*-(*p*-nitrocinnamyl)morpholine (99 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 1.0 mmol), using MgI<sub>2</sub> (334 mg, 1.2 mmol), ArCl<sub>2</sub>-PMPBox **2c** (597 mg, 1.2 mmol), and *i*-Pr<sub>2</sub>NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 82% yield (136 mg, 0.33 mmol); *syn:anti* 99:1; *syn* 97% ee. *Syn* isomer: IR (thin film) 3061, 2968, 2911, 2854, 1737, 1649, 1519, 1457, 1436, 1348, 1239 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.14 (d,  $J$  = 8.8 Hz, 2H, (NO<sub>2</sub>)PhH), 7.35 (d,  $J$  = 8.8 Hz, 2H, (NO<sub>2</sub>)PhH), 7.21-7.25 (m, 3H, CH<sub>2</sub>PhH), 6.99 (d,  $J$  = 7.7 Hz, 2H, CH<sub>2</sub>PhH), 5.94 (ddd,  $J$  = 8.8, 10.4, 17.0 Hz, 1H, CH=CH<sub>2</sub>), 5.08-5.18 (m, 2H, CH=CH<sub>2</sub>), 4.52 (d,  $J$  = 12.1 Hz, 1H, CH<sub>2</sub>Ph), 4.44 (d,  $J$  = 9.6 Hz, 1H, CHOBn), 4.27 (d,  $J$  = 11.8 Hz, 1H, CH<sub>2</sub>Ph), 3.87 (dd,  $J$  = 9.1, 9.1 Hz, 1H, CH-CH=CH<sub>2</sub>), 3.51-3.76 (m, 8H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  168.0, 147.8, 146.6, 136.1, 135.1, 129.1, 128.3, 128.0, 127.8, 123.5, 118.7, 81.8, 72.0, 67.0, 66.6, 53.0, 45.6, 42.7; HRMS (CI) exact mass calcd for (C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub> + H<sup>+</sup>) requires  $m/z$  397.1763, found  $m/z$  397.1756; [ $\alpha$ ]<sub>D</sub> = +4.0 (c = 1.0, CHCl<sub>3</sub>).

The enantiomeric purity and diastereomer ratio were determined by HPLC with a Chiralcel AD column and AD guard column (15% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer,  $t_r$  = 16.7 min and  $t_r$  = 26.1 min; *anti* isomer,  $t_r$  = 21.9 min and 29.5 min.

**(2*S*,3*S*)-*N*-(2-Benzoyloxy-3-(ethoxycarbonyl)-4-pentenoyl)-morpholine** (Table 3, Entry 6)

Prepared by the general procedure from (*E*)-ethyl 4-morpholinocrotonate (74 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 1.0 mmol), using MgI<sub>2</sub> (334 mg, 1.2 mmol), ArCl<sub>2</sub>-PMPBox **2c** (597 mg, 1.2 mmol), and *i*-Pr<sub>2</sub>NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 84% yield (111 mg, 0.32 mmol); *syn:anti* 97:3; *syn* 96% ee. *Syn* isomer: IR (thin film)

2968, 2916, 2864, 1737, 1649, 1457, 1441  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27-7.37 (m, 5H, PhH), 5.75 (ddd,  $J = 9.1, 10.1, 17.1$  Hz, 1H,  $\text{CH}=\text{CH}_2$ ), 4.61 (d,  $J = 11.7$  Hz, 1H,  $\text{CH}_2\text{Ph}$ ), 4.60 (d,  $J = 10.5$  Hz, 1H,  $\text{CH}-\text{OBn}$ ), 4.51 (d,  $J = 11.7$  Hz, 1H,  $\text{CH}_2\text{Ph}$ ), 4.11-4.25 (m, 2H,  $\text{OCH}_2\text{CH}_3$ ), 3.50-3.65 (m, 9H,  $\text{CH}-\text{CH}=\text{CH}_2$ ),  $\text{N}(\text{CH}_2\text{CH}_2)_2$ ), 1.24 (t,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 167.6, 136.9, 130.7, 128.4, 128.1, 128.1, 120.6, 79.4, 72.3, 67.0, 66.7, 61.2, 54.0, 45.7, 42.5, 14.1; HRMS (CI) exact mass calcd for ( $\text{C}_{19}\text{H}_{25}\text{NO}_5 + \text{H}^+$ ) requires  $m/z$  348.1811, found  $m/z$  348.1804;  $[\alpha]_{\text{D}} = -31.8$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

The enantiomeric purity and diastereomer ratio were determined by HPLC with a Chiralcel AD column and AD guard column (10% EtOH:hexanes, 1 mL/min flow); *syn* isomer,  $t_{\text{r}} = 15.5$  min and 20.6 min; *anti* isomer,  $t_{\text{r}} = 14.1$  min and 19.5 min.

**(2S,3R)-N-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine** (Table 3, Entry 7) Prepared by the general procedure from (*E*)-*N*-(3-chloro-2-propenyl)morpholine (65 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 1.0 mmol), using  $\text{MgI}_2$  (334 mg, 1.2 mmol),  $\text{ArCl}_2\text{-PMPBox } \mathbf{2c}$  (597 mg, 1.2 mmol), and *i*-Pr<sub>2</sub>NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 95% yield (118 mg, 0.38 mmol); *syn:anti* 98:2; 91% ee.  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR, and mass spectral data for this compound were consistent with those previously reported.<sup>5</sup>  $[\alpha]_{\text{D}} = -5.8$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ). The enantiomeric purity was determined by HPLC with a Chiralcel OJ column and OJ guard column (10% EtOH:hexanes, 0.5 mL/min); *syn* isomer,  $t = 53.0$  min and  $t = 61.5$  min. The diastereomer ratio was determined by GC with a CC-1701 column (70 °C, 7 °C/min gradient, 1 mL/min); *syn* isomer,  $t_{\text{r}} = 29.8$  min, *anti* isomer,  $t_{\text{r}} = 30.3$  min.

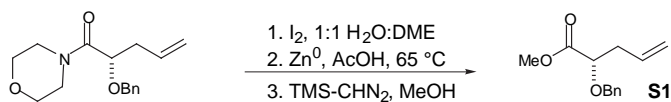
**(2S,3S)-N-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine** (Table 3, Entry 8) Prepared by the general procedure from (*Z*)-*N*-(2-phenyl-2-propenyl)morpholine (81 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 1.0 mmol), using  $\text{MgI}_2$  (334 mg, 1.2 mmol),  $\text{ArCl}_2\text{-PMPBox}$

**2c** (597 mg, 1.2 mmol), and *i*-Pr<sub>2</sub>NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 79% yield (111 mg, 0.32 mmol). <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, and mass spectral data for this compound were consistent with those previously reported.<sup>5</sup> [ $\alpha$ ]<sub>D</sub> = +54.9 (c = 1.0, CHCl<sub>3</sub>). The enantiomeric purity and diastereomer ratio were determined by HPLC with a Chiralcel OJ column and OJ guard column (6%:1% *i*-PrOH:EtOH:hexanes, 1 mL/min flow); *anti* isomer, *t*<sub>r</sub> = 37.6 min and 51.0 min; *syn* isomer, *t*<sub>r</sub> = 48.2 min.

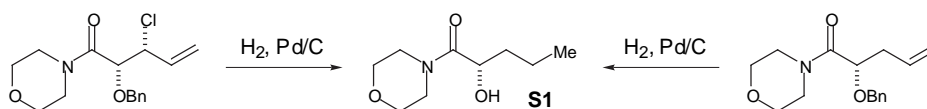
**(2*S*,3*S*)-N-(2-Benzoyloxy-3-(ethoxycarbonyl)-3-methyl-4-pentenoyl)-morpholine (5).** Prepared by the general procedure from ethyl (*E*)-4-morpholino-2-methylcrotonate (85 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 1.0 mmol), using MgI<sub>2</sub> (334 mg, 1.2 mmol), ArCl<sub>2</sub>-PMPBox **2c** (597 mg, 1.2 mmol), and *i*-Pr<sub>2</sub>NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 75% yield (109 mg, 0.30 mmol); *syn:anti* 94:6; *syn* 97% ee. IR (thin film) 3093, 3051, 2968, 2906, 2854, 1732, 1654, 1457, 1441, 1239 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz)  $\delta$  7.26-7.34 (m, 5H, Ph), 5.94 (dd, *J* = 10.7, 17.3 Hz, 1H, CH=CH<sub>2</sub>), 5.11-5.18 (m, 2H, CH=CH<sub>2</sub>), 4.76 (s, 1H, CHOBn), 4.59 (d, *J* = 11.8 Hz, CH<sub>2</sub>Ph), 4.43 (d, *J* = 11.8 Hz, CH<sub>2</sub>Ph), 4.06-4.21 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 3.34-3.60 (m, 8H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 1.44 (s, 3H, CH<sub>3</sub>), 1.21 (t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  173.0, 167.2, 137.1, 136.8, 128.2, 127.9, 127.9, 116.3, 79.2, 72.5, 67.0, 66.4, 61.3, 53.9, 46.4, 42.4, 15.4, 14.1; HRMS (CI) exact mass calcd for (C<sub>20</sub>H<sub>27</sub>NO<sub>5</sub> + H<sup>+</sup>) requires *m/z* 362.1967, found *m/z* 362.1960; [ $\alpha$ ]<sub>D</sub> = -33.6 (c = 1.0, CHCl<sub>3</sub>).

The enantiomeric purity and diastereomer ratio were determined by HPLC with a Chiralcel AD column and AD guard column (6% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer, *t*<sub>r</sub> = 15.7 min and 17.6 min; *anti* isomer, *t*<sub>r</sub> = 16.5 min.

<sup>5</sup> Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726.



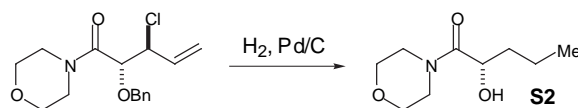
**Determination of the absolute configuration of (2*S*)-*N*-(2-benzyloxy-4-pentenyl)-morpholine by correlation with (2*S*)-2-benzyloxy-4-pentenoic acid methyl ester (S1).** A solution of (2*S*)-*N*-(2-benzyloxy-4-pentenyl)-morpholine (23 mg, 84  $\mu$ mol) in 2 mL 1:1 water/ DME was placed in an 8 mL scintillation vial equipped with a magnetic stir bar. The solution was treated with iodine (53 mg, 0.21 mmol) and stirred at 23 °C for 10 min. The reaction was then quenched with 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (1 mL) and extracted into  $\text{Et}_2\text{O}$ . The resulting organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The unpurified iodolactone product was then taken up in glacial AcOH (1 mL). The resulting solution was then treated with zinc dust (55 mg, 0.84 mmol) and stirred at 65 °C for 1.5 h. Upon cooling to ambient temperature, 1 *N* HCl (aq) (1 mL) was added, and the resulting mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 1 mL). The organic extracts were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The resulting carboxylic acid was then taken up in MeOH and TMS- $\text{CHN}_2$  (2.0 M in hexanes) was added dropwise until a bright yellow color persisted. The reaction was then treated with a drop of AcOH and concentrated. The residue was purified by flash chromatography (5:1 hexanes:EtOAc) to afford 9.5 mg (43  $\mu$ mol, 52% yield) of a clear oil that was spectroscopically identical in all respects to the compound (2*S*)-2-benzyloxy-4-pentenoic acid methyl ester.<sup>6</sup>  $[\alpha]_{\text{D}}$  (literature) = +46 ( $c = 1.0$ ,  $\text{CHCl}_3$ );  $[\alpha]_{\text{D}}$  (observed) = +55 ( $c = 1.0$ ,  $\text{CHCl}_3$ ).



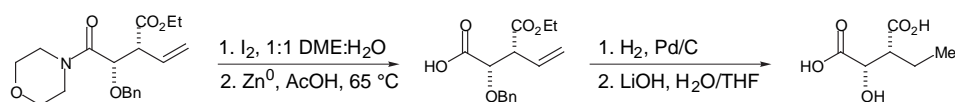
**Determination of the absolute stereochemistry of (2*S*,3*S*)-*N*-(2-benzyloxy-3-chloro-4-pentenyl)-morpholine by correlation with (2*S*)-*N*-(2-hydroxypentanoyl)-morpholine (S1).** A suspension containing (2*S*)-*N*-(2-benzyloxy-4-pentenyl)-morpholine (19 mg, 68  $\mu$ mol) of known absolute configuration (*vide supra*) and 10% palladium on carbon (25 mg) in 1 mL ethanol was stirred under an atmosphere of  $\text{H}_2$  for 30 min. The catalyst was removed by filtration through a short plug of

celite, and the filtrate was concentrated. Purification of the residue by flash chromatography (1:1 hexanes:EtOAc) afforded 12 mg (68  $\mu$ mol, 96% yield) of a colorless film.  $[\alpha]_D = +4.0$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

A suspension containing of (2*S*,3*S*)-*N*-(2-benzyloxy-3-chloro-4-pentenoyl)-morpholine (43 mg, 0.14 mmol) and 10% palladium on carbon (50 mg) in EtOH (2 mL) was stirred under at atmosphere of  $\text{H}_2$  for 1 h. The catalyst was then removed by filtration through a short plug of celite, and the filtrate was concentrated. Purification of the residue by flash chromatography (1:1 hexanes:EtOAc) afforded 25.4 mg (0.14 mmol, 97%) of a colorless oil that was spectroscopically identical to **S1** in all respects.  $[\alpha]_D = +2.4$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).



**Determination of the absolute stereochemistry of (2*S*,3*R*)-*N*-(2-benzyloxy-3-chloro-4-pentenoyl)-morpholine by correlation with (2*S*)-*N*-(2-hydroxypentanoyl)-morpholine (**S2**).** A suspension containing of (2*S*,3*R*)-*N*-(2-benzyloxy-3-chloro-4-pentenoyl)-morpholine (26.2 mg, 84.6  $\mu$ mol) and 10% palladium on carbon (50 mg) in EtOH (2 mL) was stirred under at atmosphere of  $\text{H}_2$  for 1.5 h. The catalyst was then removed by filtration through a short plug of celite, and the filtrate was concentrated. Purification of the residue by flash chromatography (1:1 hexanes:EtOAc) afforded 15 mg (81  $\mu$ mol, 96% yield) of a colorless film that was spectroscopically identical to **S2**.  $[\alpha]_D = +1.0$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).



**Determination of the absolute stereochemistry of (2*S*,3*S*)-*N*-(2-benzyloxy-3-(ethoxycarbonyl)-4-pentenoyl)-morpholine by correlation with (2*S*,3*R*)-3-ethylmalic acid.** A solution of (2*S*,3*S*)-*N*-(2-benzyloxy-3-(ethoxycarbonyl)-4-pentenoyl)-morpholine (34 mg, 0.1 mmol) in 2.4 mL 1:1  $\text{H}_2\text{O}$ /DME was treated with iodine (64 mg, 0.25 mmol) and stirred at 23  $^\circ\text{C}$  for 1 h. The resulting solution

<sup>6</sup> Kato, Y.; Ohta, H.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, 28, 1303.

was then treated with 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (1 mL) and extracted into  $\text{Et}_2\text{O}$ . The resulting organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The iodolactone residue was then taken up in glacial  $\text{AcOH}$  (2.5 mL) and treated with zinc dust (65 mg, 1.0 mmol) and stirred at 65 °C for 1.5 h. Upon cooling to ambient temperature, 1 *N*  $\text{HCl}$  (aq) (1 mL) was added, and the mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 1 mL). The organic extracts were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and then concentrated.

The resulting carboxylic acid was taken up in THF (4 mL) and treated with 10% palladium on carbon (50 mg) and stirred under an  $\text{H}_2$  atmosphere for 1 h. The catalyst was then removed by filtration through a short plug of celite, and the filtrate was concentrated. The resulting residue was then taken up in 3:1 THF: $\text{H}_2\text{O}$  (4 mL) and treated with  $\text{LiOH}\cdot\text{H}_2\text{O}$  (42 mg, 1.0 mmol). The solution was warmed to 65 °C for 14 h. After cooling to ambient temperature, the reaction mixture was added to Dowex 50X80-200 ( $\text{H}^+$  form) resin. The resin was removed by filtration and washed with  $\text{H}_2\text{O}$ . The combined filtrate was concentrated to afford 7 mg of a yellow oil (43  $\mu\text{mol}$ , 43% for 4 steps) that was identical to (2*R*,3*S*)-3-ethylmalic acid<sup>7</sup> in all regards except for optical rotation, which was opposite in sign.  $[\alpha]_{\text{D}}$  (literature) = -3.1 (*c* = 1.0,  $\text{H}_2\text{O}$ );  $[\alpha]_{\text{D}}$  (observed) = +1.4 (*c* = 1.0,  $\text{H}_2\text{O}$ ).

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<sup>7</sup> Kakinuma, K.; Terasawa, H.; Li, H.-Y.; Miyazaki, K.; Oshima, T. *Biosci. Biotech. Biochem.*, **1993**, 57, 1916.